

## Real-World Association Between mRNA Vaccination and Infection From the Omicron Strain of SARS-CoV-2: A Population-Level Analysis



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**Introduction:** Two mRNA vaccines approved in the U.S. have high efficacy against COVID-19 disease from the original strain of SARS-CoV-2. We evaluated the population-level association between vaccination status and COVID-19 infection by age group during the initial wave of the Omicron variant in a diverse population in the Mid-South U.S.

**Methods:** In this observational population-based cohort study, vaccination information and positive COVID-19 cases in Shelby County, Tennessee, from December 12, 2021 through January 22, 2022 were collected from surveillance data at the Shelby County Health Department (Memphis, Tennessee). Exposure groups included individuals who were unvaccinated, were fully vaccinated, and were fully vaccinated + booster. We calculated incidence rates of COVID-19 diagnosis per person-year among county adult (aged 18+ years) residents in crude form and stratified by age group.

**Results:** In this population-based study, we identified 64.56% fewer COVID-19 infections in the fully vaccinated + booster group and 41.08% fewer in the fully vaccinated group than in the unvaccinated group.

**Conclusions:** These results confirm and extend the findings of recent immunologic and epidemiologic studies in a racially diverse region of the Mid-South U.S. In stratified analysis, we also found evidence suggesting that vaccine protection against Omicron may increase with age.

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## INTRODUCTION

Two mRNA vaccines approved in the U.S. have high efficacy against coronavirus disease 2019 (COVID-19) from the original strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1,2</sup> Early immunologic and epidemiologic studies suggest that mRNA vaccines provide attenuated protection against the Omicron (B.1.1.529) variant, with individuals who received a third vaccine dose having the most protection.<sup>3,4</sup> We evaluated the population-level association between vaccination status and state-reported COVID-19 infection

by age group during the initial wave of the Omicron variant in a diverse population in the Mid-South U.S.

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## METHODS

In this observational population-based cohort study, vaccination information and positive COVID-19 cases in Shelby County, Tennessee, from December 12, 2021 through January 22, 2022 were collected from surveillance data at the Shelby County Health Department (Memphis, Tennessee). During this period, 90.5% of the sequenced COVID-19 tests were the Omicron variant. Daily case files reported to the Shelby County Health Department from the Tennessee Department of Health include all resident cases identified through a reported positive test result (i.e., polymerase chain reaction, antigen, or serology testing). Daily vaccination files from the Tennessee Immunization Information System include COVID-19 vaccination information for Shelby County residents. This vaccine surveillance data include all reported information about products and doses received, administration dates, and location of administration for COVID-19 vaccination of residents of Shelby County.

Exposure groups included individuals who received no vaccine for COVID-19 (unvaccinated), who were fully vaccinated with 2-dose mRNA COVID-19 vaccine series and no additional dose (fully vaccinated), and who were fully vaccinated with 2-dose mRNA COVID-19 vaccine series and received an additional dose (fully vaccinated + booster). Those with >1 additional dose were included in the fully vaccinated + booster group. We excluded a small number who received non-mRNA COVID-19 vaccines. Those who were vaccinated with a non-mRNA COVID-19 vaccine option for their first or second dose did not contribute time to the fully vaccinated group or to the fully vaccinated + booster group. In this case, adults contributed time to the unvaccinated group until their first COVID-19 vaccination, if applicable, after which they were censored. In addition, those who were fully vaccinated with an mRNA COVID-19 vaccine and were vaccinated with a non-mRNA COVID-19 vaccine option for their third dose did not contribute time to the fully vaccinated + booster group. In this case, time was contributed to the fully vaccinated group until the date of the additional dose. Because case surveillance and vaccine records include individual-level data about residents who have become a case or been vaccinated but do not include the status of residents who have not become a reported case or been vaccinated, we estimated total population numbers with the 2020 National Center for Health Statistics estimates.<sup>5,6</sup>

We calculated incidence rates of COVID-19 diagnosis per person-year of follow-up time among adults on the basis of study timeframe, individual vaccination dates, and individual diagnosis dates (individuals could contribute person-years to multiple groups). Incidence rates and incidence rate ratios (IRRs) along with 95% CI were calculated in crude form for those aged

≥18 years and by age group (18–34, 35–64, ≥65 years) using an alpha of 0.05. Incidence rates with exact 95% CI were calculated with epiR (R, version 4.1), and IRRs with Wald 95% CI were calculated with epitools (R, version 4.1). Sensitivity analyses were conducted to quantify the potential impact of several situations of bias on the estimates. These analyses assessed the impact of various potential sources of bias, including under- or over-representation of the true population by the population estimates, misclassification of person-time by vaccination status, and under-reporting of COVID-19 infection. This report uses STROBE guidelines with oversight from the University of Memphis IRB (PRO-FY2022-317).

## RESULTS

Our study population has approximately 703,648 adults with a racial distribution of 37.8% White, 50.1% Black, 3.1% Asian, and 9.0% other/multiple. In total, 207,364 adults contributed 21,287.21 person-years to the unvaccinated group, 292,149 adults contributed 27,809.97 person-years to the fully vaccinated group, and 168,589 adults contributed 16,408.21 person-years to the fully vaccinated + booster group (Table 1). Vaccine status was significantly associated with age group ( $p < 0.0001$ ) (Table 1). In total, vaccinated time was not contributed for 18,195 adults who received a non-mRNA vaccine for their first or second dose, and time was not contributed to the fully vaccinated + booster group for 262 adults who were fully vaccinated with an mRNA vaccine but received a non-mRNA vaccine for their third dose.

Overall, 48,669 cases of COVID-19 were identified in adults (aged ≥18 years): 23,823 in unvaccinated, 18,338 in fully vaccinated, and 6,508 in fully vaccinated + booster groups. Fully vaccinated persons had a 41.08% lower incidence of COVID-19 than unvaccinated persons (IRR=0.589, 95% CI=0.578, 0.601), and those who were in the fully vaccinated + booster group had a 64.56% lower incidence of COVID-19 than the unvaccinated group (IRR=0.354, 95% CI=0.345, 0.364) (Table 2 and Table 3). Stratified by age group, the strongest effect was observed in the fully vaccinated + booster group versus the unvaccinated group in persons aged ≥65 years (IRR=0.191, 95% CI=0.178, 0.205), decreasing

**Table 1.** Numbers of Contributing Individuals and Total Person-Years by Vaccine Status and Age Group

Age group, years	Unvaccinated, total individuals (total person-years)	Fully vaccinated, total individuals (total person-years)	Fully vaccinated + booster, total individuals (total person-years)
18–34	106,330 (11,007.15)	83,722 (8,138.22)	21,762 (1,903.51)
35–64	86,957 (8,854.47)	158,633 (14,947.97)	84,122 (7,962.39)
≥65	14,077 (1,425.60)	49,794 (4,723.78)	62,705 (6,542.31)
Overall ≥18	207,364 (21,287.21)	292,149 (27,809.97)	168,589 (16,408.21)

Note: Vaccine status at the start of the study was significantly associated with age group (chi-square  $p < 0.0001$ ).

**Table 2.** Incidence Rates Per Person-Year of Follow-Up Time and Incidence Rate Ratios by Vaccination Status and Age Group

Age group, years	Unvaccinated, incidence rate (95% CI)	Fully vaccinated, incidence rate (95% CI)	Fully vaccinated + booster, incidence rate (95% CI)		Fully vaccinated versus unvaccinated, incidence rate ratio (95% CI)	Fully vaccinated + booster versus unvaccinated, incidence rate ratio (95% CI)
			incidence rate (95% CI)	incidence rate (95% CI)		
18–34	1.014 (0.995, 1.033)	0.796 (0.777, 0.816)	0.628 (0.593, 0.664)	0.785 (0.761, 0.809)	0.619 (0.583, 0.657)	0.388 (0.374, 0.402)
35–64	1.238 (1.215, 1.261)	0.685 (0.672, 0.698)	0.480 (0.465, 0.495)	0.553 (0.539, 0.568)	0.191 (0.178, 0.205)	0.354 (0.345, 0.364)
≥65	1.194 (1.138, 1.252)	0.344 (0.327, 0.361)	0.228 (0.217, 0.240)	0.288 (0.269, 0.308)		
Overall ≥18	1.119 (1.105, 1.133)	0.659 (0.650, 0.669)	0.397 (0.387, 0.406)	0.589 (0.578, 0.601)		

Note: Incidence rates are unadjusted and calculated per person-year of follow-up time. Fully vaccinated + booster denotes fully vaccinated with a 2-dose mRNA vaccine series and received an additional dose, fully vaccinated denotes fully vaccinated with a 2-dose mRNA vaccine series and no additional dose (vaccinated), and unvaccinated denotes received no FDA-authorized vaccine for COVID-19. Age groups were chosen on the basis of similarity of the percent of the population fully vaccinated (with or without booster) as of the first day of follow-up, as reported by the Shelby County Health Department.

FDA, Food and Drug Administration.

in persons aged 35–64 years (IRR=0.388, 95% CI=0.374, 0.402) and in those aged 18–34 years (IRR=0.619, 95% CI=0.583, 0.657). We observed a similar pattern in fully vaccinated versus in unvaccinated adults by age group (Table 2). Several sensitivity analyses quantified the potential impact of bias on the estimates, showing that moderate amounts of bias are not likely to substantially impact results. This analysis also shows situations of more extreme bias and the impacts on estimates. Situations where bias could have substantially impacted results appear unlikely (Table 4).

### DISCUSSION

In this population-based study, we identified 64.56% fewer COVID-19 infections with a 2-dose mRNA vaccine series plus an additional dose and 41.08% fewer in fully vaccinated adults receiving only 2 mRNA doses than in unvaccinated adults. These results confirm and extend the findings of recent immunologic and epidemiologic studies showing attenuated protection from mRNA vaccines against the Omicron variant compared with previously circulating variants,<sup>3</sup> with increased protection seen by those vaccinated with an additional dose,<sup>3,4,7</sup> in a racially diverse region of the Mid-South U.S. We found evidence of higher vaccine effectiveness estimates among those aged ≥65 years than among younger age groups. We also found lower incidence rates among both vaccinated exposure groups than not only among the unvaccinated group of the same age but also among the same vaccination exposure group in the younger age groups. These findings suggest that vaccine protection against Omicron may increase with age. However, because these analyses are unadjusted, future analyses considering potentially confounding effects of additional demographic and behavioral factors would be useful for further assessment of the association between vaccine protection and age.

Two previous studies utilizing test-negative designs from England and the U.S. have adjusted for age in their analysis of vaccine effectiveness against the Omicron variant but not reported effectiveness measures stratified by age group.<sup>4,7</sup> A study of vaccine effectiveness against symptomatic disease using a nested test-negative design in a highly vaccinated group in Scotland conducted analysis separately for those aged 16–49 and ≥50 years. They did not find large differences in vaccine effectiveness estimates of a booster dose against symptomatic Omicron infection between the 2 age groups.<sup>8</sup> Our study is more general because we are estimating the protection that vaccination affords against diagnosed COVID-19 cases during the Omicron wave, including both symptomatic infection and nonsymptomatic infection

**Table 3.** Vaccine Effectiveness Percentage Estimates by Vaccination Status and Age Group

Age group, years	Fully vaccinated versus unvaccinated, vaccine effectiveness percentage estimate (95% CI)	Fully vaccinated + booster versus unvaccinated, vaccine effectiveness percentage estimate (95% CI)
18–34	21.51 (19.08, 23.88)	38.07 (34.29, 41.71)
35–64	44.66 (43.15, 46.13)	61.22 (59.77, 62.63)
≥65	71.22 (69.19, 73.11)	80.90 (79.52, 82.18)
Overall ≥18	41.08 (39.93, 42.20)	64.56 (63.58, 65.52)

Note: Vaccine effectiveness percentage estimates are calculated as  $(1 - \text{incidence rate ratio}) \times 100$ .

**Table 4.** Sensitivity Analysis and Impact on IRRs

Analysis factors	Fully vaccinated versus unvaccinated, IRR (95% CI)	Fully vaccinated + booster versus unvaccinated, IRR (95% CI)
Primary results	0.589 (0.578, 0.601)	0.354 (0.345, 0.364)
Increase population estimate by average annual population change: 2015–2019	0.595 (0.583, 0.606)	0.358 (0.348, 0.368)
Decrease population estimate by average annual population change: 2015–2019	0.586 (0.575, 0.597)	0.353 (0.343, 0.362)
Address 10% differential misclassification of fully vaccinated and fully vaccinated + booster time as unvaccinated	0.505 (0.496, 0.515)	0.311 (0.302, 0.319)
Address 10% differential misclassification of unvaccinated time as fully vaccinated and fully vaccinated + booster, respectively	0.778 (0.764, 0.794)	0.468 (0.455, 0.481)
Address nondifferential under-reporting of COVID-19 infection by increasing cases by 50% in each group	0.591 (0.581, 0.600)	0.355 (0.347, 0.363)
Address differential under-reporting of COVID-19 infection by increasing cases by 60% in vaccinated and 40% in unvaccinated	0.675 (0.664, 0.685)	0.406 (0.397, 0.415)
Address differential under-reporting of COVID-19 infection by increasing cases by 40% in vaccinated and 60% in unvaccinated	0.517 (0.509, 0.525)	0.311 (0.304, 0.318)
Address differential under-reporting of COVID-19 infection by increasing cases by 25% in vaccinated and 50% in unvaccinated	0.492 (0.484, 0.500)	0.296 (0.289, 0.303)
Address differential under-reporting of COVID-19 infection by increasing cases by 15% in vaccinated and 25% in unvaccinated	0.543 (0.534, 0.553)	0.327 (0.319, 0.335)

IRR, incidence rate ratio.

diagnosed through screening in a population where vaccination rate varies heavily across age groups.

The impact of age and potential confounding by behavioral mitigation and exposure patterns is an area for additional investigation. Our ability to draw definitive conclusions is limited by the nonrandomized observational design and use of population estimates for noncases. Under- or over-representation of the population estimates, misclassification of person-time by vaccination status, and under-reporting of COVID-19 cases are several factors that could have introduced bias, given the nature of the data for this study. However, sensitivity analyses showed that moderate amounts of bias from

these sources are not likely to substantially impact the results of this study. Limitations notwithstanding, our findings validate the utility of mRNA vaccination against the Omicron variant of SARS-CoV-2 in a real-world population in the Mid-South U.S. and support continued public health efforts to provide booster mRNA vaccine doses.

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## CREDIT AUTHOR STATEMENT

Allison P. Plaxco: Conceptualization, Formal analysis, Writing — original draft. Jennifer M. Kmet: Supervision, Writing — review and editing. Vikki G. Nolan: Supervision, Writing — review and editing. Michelle A. Taylor: Supervision, Writing — review and editing. Matthew P. Smeltzer: Conceptualization, Formal analysis, Writing — original draft.

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